

Influence of Excessive Weight Gain on Maternal and Perinatal Morbidity and Mortality in a University Hospital Environment in Cotonou

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Abstract

Introduction: The pathologies associated with excessive weight gain during pregnancy are numerous and frequent. They are the cause of significant maternal and perinatal morbidity and mortality and thus pose a real public health problem. **Patients and method:** The main objective of our work was to study the influence of excessive weight gain on maternal and perinatal morbidity and mortality in a university hospital in Cotonou. **Study method:** The study took place at the CUGO. This was a descriptive and analytical study with retrospective data collection over a period of 10 years from January 1, 2012 to December 31, 2021. The analysis focused on the description of pregnant women and the search for factors associated with an excessive weight gain during pregnancy and which influence maternal and perinatal prognosis. The different odds ratios and their confidence intervals were calculated. The significance level was 5%. **Results:** A total of 690 pregnant women were included and divided into four sub-populations according to their pre-gestational or first trimester BMI: 05.94% underweight pregnant women, 41.74% normal BMI pregnant women, 28.55% of overweight pregnant women and 23.77% obese pregnant women. The average age of pregnant women was 30.41 years \pm 5.40 years. They were civil servants (35.80%) and resided in Cotonou in 93.91% of cases. Pregnant women had a history of hypertension in nearly 3% of cases. Pregnancy hypertension (07.97%) was the main pathology associated with pregnancy in our study. Weight gain was excessive in overweight pregnant women and obese pregnant women in the same proportion 41.12%. The average weight gain was 9.42 kg for underweight pregnant women, 8.35 kg for pregnant women with a normal BMI, 8.46 kg for overweight pregnant women and 7.45 kg for obese pregnant women. Pregnant women who had gained ex-

cessive weight during pregnancy had a 9 times higher risk of having pregnancy-induced hypertension (OR = 9.5 and $p \leq 0.0001$). They also presented a 6 times higher risk of having pre-eclampsia (OR = 6.6; $p \leq 0.0001$). The risk of gestational diabetes is also high (OR = 3.82; $p \leq 0.0001$). There is also a risk of macrosomia (OR = 3.33 and $p = 0.007$) and the risk of cesarean delivery 2 times higher: OR = 2.15 and $p = 0.0004$. There was no statistically significant link between excessive weight gain and term at delivery, the condition of the newborn at birth, and neonatal mortality. **Conclusion:** Excessive weight gain during pregnancy in our study was assessed in several pregnant women with a high prevalence. It is the source of several maternal and fetal complications.

Keywords

Pregnancy, Weight, Nutrition, Morbidity, Motatlity

1. Introduction

During gestation, the body undergoes obvious physical transformations concomitant with significant psychological reorganization in order to prepare for parenthood [1]. Weight gain during pregnancy is a physiological event. It is linked on the one hand to the growth of fetal tissues and on the other hand to maternal metabolic changes. However, it happens that this physiological phenomenon becomes a pathology. Indeed, more and more pregnant women are gaining excessive weight during pregnancy. The 2016 national perinatal survey reported that 48% of women studied had excess weight gain during pregnancy [2]. Taking maternal weight is therefore a good short- and long-term predictor of the health of pregnant women and their children [3]. Weight status is a hot topic and a public health issue. Overweight and obesity are chronic diseases and constitute serious public health problems because they are the cause of many physical and psychological complications that can affect the course of pregnancy. Epidemiological studies have shown that the most important weight gains are associated with maternal imbalances in prenatal blood sugar levels, and complications during childbirth, as well as difficulties in losing weight after childbirth [3]. It is indeed now well recognized that gestational weight gain directly influences intrauterine growth: an infant whose mother has had significant gestational weight gain is unlikely to be small or to have a low birth weight [4] [5]. A systematic review of cohort studies shows that women with hyperglycemia (gestational diabetes) detected during pregnancy have a higher risk of adverse pregnancy outcomes, including macrosomia, and shoulder dystocia [6]. In sub-Saharan Africa, data on the obstetrical repercussions of obesity are rare [7]. In Benin, a study carried out in a population of pregnant women at the reference university hospital of Cotonou in 2002 found diabetes mellitus, cesarean delivery, macrosomia associated with obesity [8]. The objective of this present work is therefore to analyze the influence of excessive weight gain on maternal and perinatal mor-

bidity and mortality. To our knowledge, few studies have been devoted to this subject. Nevertheless, a study was carried out on “The influence of maternal weight on the evolution of pregnancy in pregnant women in the city of Parakou in 2015 in Benin”. Note that this study was only interested in the weight profile at the start of pregnancy and did not take into account weight monitoring throughout the course of pregnancy. Our study will have the particularity of taking into account the weight profile through each trimester of gestation in order to better establish a correlation between the occurrences of complications. It will show the importance of weight monitoring during pregnancy, as well as the complications that may be associated with excessive weight gain during pregnancy in order to be able to raise awareness among pregnant women and to be able to prevent certain complications for a smooth pregnancy.

2. Method Study

The study took place at the University Clinic of Gynecology and Obstetrics (CUGO), and in the neonatology department of the Center National Hospitalier et Universitaire Hubert Koutoukou Maga (CNHU-HKM).

This was a descriptive and analytical study with retrospective data collection over a period of 10 years from January 1, 2012 to December 31, 2021. The study focused on the medical records of pregnant women followed and having given birth at CUGO as well as on the records of their newborns during the study period. The inclusion criteria were all the records of pregnant women who followed their pregnancy at the CUGO, and who had their first prenatal consultation (CPN) in the first trimester and for whom the pre-gestational weight in the first trimester is available as well as the height. Records of women with premature babies and miscarriages were not included. We carried out an exhaustive recruitment of all files meeting the inclusion and non-inclusion criteria over the study period.

We have developed a collection sheet. The variables studied were weight gain during pregnancy, socio-demographic data of patients, age at diagnosis, patient's profession, history: diabetes, macrosomia, dystocia, general parameters: weight at each prenatal consultation, height, pre-gestational BMI and BMI and in the 1st trimester, ultrasound signs: a weight greater than the 90th percentile for gestational age and an abdominal circumference greater than 350 mm raise suspicion of fetal macrosomia. After counting, the data was entered using Epi Data 3.1 software. As for the data analysis, it was conducted with the STATA version 13 software. The comparison of the means was made with the Student test, that of the frequencies with the Chi² test. The statistical significance threshold is less than 5%. The quantitative variables were described by the mean with a calculation of the standard deviation. The description of the qualitative variables was made in proportion to their confidence interval. Weight change curves were described through corpulence trajectories. Factors associated with excessive weight gain were described by a binary logistic regression model. The independent effects of

excessive weight gain on the occurrence of maternal and perinatal complications were identified using a binary logistic regression model by adjusting for potential confounding factors. Optimal weight gain was determined using Bayesian inferences with the probability of minimizing the occurrence of complications.

3. Results

3.1. Socio-Demographics Characteristics

- Age of pregnant women

The table below summarizes the distribution of pregnant women according to age (**Table 1**).

The mean age of the patients was 30.41 years \pm 5.40 years. The youngest pregnant woman in our sample was 16 years old and the oldest was 45 years old.

- Characteristics of pregnancies.

- Gestational age at first prenatal consultation.

The mean term at the first prenatal consultation was 11.73 \pm 3.70 SA.

- Pathologies associated with pregnancy.

3.2. Distribution of Pregnant Women According to Pathologies Associated with Their Pregnancy

We have presented in **Table 2** the pathologies associated with pregnancy.

One hundred and thirty-four pregnant had presented at least one pathology associated with pregnancy. Obstetrically, pregnancy-induced hypertension (07.97%) was the main associated pathology followed by premature rupture of membranes (PRM) (07.68%) and preeclampsia (02.46%). On the medical level, HIV (02.46%) was the main associated pathology followed by malaria (02.03%).

Acronym: HBP: high blood pressure; PRM: premature rupture of membranes; TNP: transversely narrowed pelvis; TPB: threat of preterm birth; HRP: hématome retro-placentaire.

We found abnormalities on ultrasound in 21 pregnant women. Macrosomia was the most found anomaly in 19 pregnant women (90.47%).

3.3. Changing Patterns of Weight Gain during Pregnancy

- Pre-gestational weight status.

Table 3 shows the distribution of pregnant women according to pre-gestational

Table 1. Age distribution of pregnant women.

	total	Percentage (%)
≤ 20	19	02.75
]20 - 30]	325	47.10
]30 - 40]	332	48.12
>40	14	02.03
Total	690	100.00

weight status.

- Average weight gain by weight status

We have presented in **Table 4**, the distribution of pregnant women according to the average gain according to weight status.

Mean weight gain during pregnancy was higher in underweight pregnant

Table 2. Associated pathologies distribution in pregnant women.

	total	Percentages (%)
Obstetrics		
Gravidic HBP	55	07,97
PRM	53	07,68
Pre-eclampsia	17	02,46
TNP	10	01,45
TPB	6	00,87
Placenta praevia	5	00,72
Eclampsia	1	00,14
HRP	3	00,43
Medical		
VIH	17	02,46
Malaria	14	02,03
Hemoglobinopathy	4	00,58
Diabète mellitus	3	00,43
none	556	80,57

Table 3. Distribution of pregnant women according to pre-gestational weight.

	total	Percentage (%)
underweight	42	06.09
Normal	288	41.74
overweight	196	28.41
Obesity	164	23.77
Total	690	100.00

Table 4. Distribution of pregnant women according to average gain according to weight.

	average	Minimum	Maximum
underweight	9.42 ± 4	3.8	24
Normal	8.35 ± 4.19	2	22
overweight	8.46 ± 5.03	1.9	32.6
Obesity	7.45 ± 3.87	1.8	20

women and lower in overweight pregnant women.

- Excessive weight gain

We have presented in **Table 5** the distribution of pregnant women having had excessive weight gain according to pre-gestational weight status.

Overweight women (41.12%) and obese women (41.12%) had much more excessive weight gain during pregnancy.

Post-operative follow-up, complications, length of hospitalization.

Planned caesareans represent 34.62% of the indications followed by prophylactic caesareans during labor which represent 30.77%. Among the pregnant women who gave birth by caesarean section, 07.97% had had complicated post-operative course. Hypertension was the most observed postoperative complication. Most of the pregnant women in general had stayed in the maternity ward for less than 4 days.

- Neonatal

We had recorded two stillbirths. Of the 690 files analyzed, the APGAR score was entered for 686 newborns at the 1st minute of life, then for 688 and 529 newborns respectively at the 5th and 10th minute of life. Forty-six children were resuscitated for more than 10 minutes. Concerning the birth weight, 81.30% of the newborns had a normal weight then 02.17% of the children presented a macrosomia. There were 44.78% of newborns who were transferred to Neonatology. Eight cases of death were recorded in neonatology. Perinatal asphyxia was the main cause of death (75%) followed by respiratory distress which was 25%.

3.4. Factors Associated with Excessive Weight Gain during Pregnancy

- Effects of excessive weight gain on maternal morbidity.

We have presented in the table below the data relating to pregnancy complications in pregnant women who have had excessive weight gain (**Table 6**).

Pregnant women who had gained excessive weight during pregnancy had a 9 times higher risk of having pregnancy-induced hypertension (OR = 9.5 and $p \leq 0.0001$). They also presented a 6 times higher risk of having pre-eclampsia (OR = 6.6; $p \leq 0.0001$). The risk of gestational diabetes is also high (OR = 3.82; $p \leq 0.0001$).

- Effects of excessive weight gain on the delivery route

Pregnant women who had gained excessive weight during pregnancy had a

Table 5. excessive weight gain according to pre-gestational or first trimester weight.

	total	Percentage (%)
underweight	1	0.93
Normal	18	16.82
overweight	44	41.12
Obesity	44	41.12
Total	107	100.00

Table 6. Excessive weight gain and pregnant complications et complications de la grossesse.

	Excessive weight gain		p-value	OR	IC95% [OR]
	yes	No			
gravidic HBP			<0.0001*		
No	76 (71.02%)	559 (95.88%)		1	
yes	31 (28.97%)	24 (04.11%)		9.5	5.29 - 17.0
Pre-eclampsia			<0.0001*		
No	98 (91.58%)	575 (98.62%)		1	
yes	9 (08.41%)	8 (01.37%)		6.6	2.48 - 17.5
Gestational diabetes			<0.0001*		
Non	104 (97.19%)	583 (100%)		1	
Oui	3 (02.80%)	0 (00.00%)		3.82	2.9 - 5.02

twice as high risk of giving birth by caesarean section with OR = 2.15 and p = 0.0004.

Influence of excessive weight gain on neonatal morbidity.

We have presented in the table below the data relating to excessive weight gain and perinatal prognosis (**Table 7**).

- Effects of excessive weight gain on neonatal prognosis

There was no statistically significant link between excessive weight gain and term at delivery, the condition of the newborn at birth or with the transfer to neonatology and neonatal mortality.

Excessive weight gain during pregnancy significantly increases the risk of macrosomia with OR = 6.24 and p = 0.0009.

4. Discussion

4.1. Factors Associated with Excessive Weight Gain during Pregnancy

Sociodemographic data

The average age of pregnant women was 30.41 years \pm 5.40 years comparable to that noted in other series such as that of Bouabida. D and col in 2018, 28 years \pm 3 years and Faye A and col in Senegal in 2010 (20 - 34 years) [9] [10]. According to the authors, these ages correspond to the period of maximum fertility in women [11]. In Africa, the age of childbearing is lower due to early marriage and the dropout of young girls. In our study, 50.46% of pregnant women who had excessive weight gain were >30 years old but without a statistically significant link with p = 0.94. However, a 2008 study in the United States of 770 women of Hispanic origin reported that pregnant women who had excessive weight gain were significantly more numerous in the 15 - 20 and 20 - 25 age groups [12]. This trend can be explained by the 2010 health and nutrition barometer report

Table 7. Excessive weight gain and perinatal prognosis.

	Excessive weight gain		p-value	OR	IC95% [OR]
	yes	No			
Term at delivery			0.45		
[37 - 41[103 (96.26%)	566 (97.08%)		1	
[41 - 42[4 (03.76%)	13 (02.22%)		1.69	0.54 - 5.2
≥42	0 (00.00%)	4 (00.68%)		0.97	0.58 - 1.6
Condition of newborn			0.17		
Born alive	106 (99.06%)	582 (99.82%)		1	
stillborn	1 (00.93%)	1 (00.17%)		5.49	0.34 - 88
APGAR first minute			0.42		
≤3	1 (00.93%)	2 (00.34%)		1	
4 - 6	13 (12.14%)	23 (03.94%)		1.13	0.09 - 13
>7	93 (96.91%)	554 (95.02%)		0.33	0.02 - 3.7
Birth weight (g)			0.0009		
<2500	11 (10.28%)	103 (17.66%)		1	
2500 - 4000	90 (84.11%)	471 (80.78%)		1.78	0.92 - 3.4
>4000	6 (5.60%)	9 (01.54%)		6.24	1.86 - 20
Neonatal deaths			0.11		
No	104 (97.19%)	578 (99.14%)		1	
yes	3 (02.80%)	5 (00.85%)		3.33	0.78 - 14

written by Inpes. This report shows that the diet of young people under 25 is less balanced than that of their elders because they consume more sugary drinks, fast food, skip more meals and do not eat enough fruit and vegetables. Young pregnant women in this age group are therefore more likely to have excessive weight gain during pregnancy, unlike pregnant women over the age of 25 who have a seemingly more balanced diet [13].

In terms of occupation/profession, 35.80% of pregnant women were civil servants and 42.17% had university studies. They mostly lived in Cotonou (93.91%). This profile of educated women, most of whom benefit from administrative support, is favorable to prenatal follow-up, which must be started in the first trimester of pregnancy. It is also usually these women who can report their weight and height before the onset of the pregnancy in accordance with our eligibility criteria. We found a statistically significant link between occupation and excessive weight gain. Civil servants were more likely than housewives to gain excessive weight, this risk was multiplied by four with an OR = 4.15 and $p < 0.0001$. This can be explained by the sedentary lifestyle observed among civil servants whose the majority of activities are limited to the desk and in a seated

position. Similarly, for some authors, data from demographic studies mainly concern the existence of a link between a low social level (ethnic minority, socioeconomic status or low level of education) and insufficient weight gain during pregnancy. [14]. Our data diverge with other studies. According to the National Institute of Health and Medical Research, the prevalence of obesity has increased in all socio-professional categories, but unevenly. It remained inversely proportional to the level of education [15]. These results can be explained by the fact that in the West the upper social classes manage to have a balanced diet.

Clinical features

In terms of history, about 3% of pregnant women had a history of hypertension. Caesarean section was the most found surgical history (34.93%). The mean term at the first ANC was 11.73 ± 3.70 SA. In terms of associated pathologies, on the obstetric level, pregnancy-induced hypertension (07.97%) was the main associated pathology followed by PMR (07.68%). Regarding hypertension, authors report in a study that 6% to 8% of pregnancies are complicated by hypertension disorders, one of the major causes of maternal and fetal morbidity [16]. These disorders include gestational hypertension (new onset hypertension without proteinuria, seen after the 20th week of pregnancy) and pre-eclampsia (new onset hypertension with proteinuria and edema after the 20th week) [16]. Several epidemiological studies have shown a direct relationship between weight gain most important during pregnancy and the onset of hypertension or pre-eclampsia [17]-[26]. In addition, weight gain less than or equal to the IOM recommendations would be protective against the onset of hypertension during pregnancy. Several other authors have described these factors and reported a significant link with excessive weight gain during pregnancy [18] [20] [23] [27].

Concerning the term at delivery, we noted a prolonged pregnancy in 02.46% of the pregnant women then the passing of term in 00.58% of the pregnant women. Our results agree with the literature data. According to the authors, women who have had excessive weight gain give birth more frequently at term. This phenomenon has already been observed in studies by Halloran, Johnson and Benchimol [28] [29] [30]. Regarding the route of delivery, the prevalence of caesarean section was estimated at 52.75%. Scheduled caesarean sections represented 18.26% of directions. On ultrasound, macrosomia was the most found anomaly (02.73%). It was also one of the indications for caesarean section. With regard to the mode of delivery of pregnant women with excessive weight gain, our results are similar to those found in the studies by Deruelle, Cadergen and Haugen which reported that women who gained too much weight during pregnancy had a higher rate of caesarean section during labor [31] [32] [33].

4.2. Influence of Excessive Weight Gain on Maternal and Perinatal Morbidity and Mortality

Weight status

Pre-gestational BMI was provided in 690 pregnant women in our study. It appears that 52.32% of pregnant women were overweight. The prevalence of ob-

esity and overweight in our study was 23.77% and 28.55% respectively. Similar data have been reported in studies carried out in the United States and Ireland which found similar prevalences of obesity to ours respectively 20% and 25.2% [13] [14]. Already in 2015, a study carried out in Parakou by Achille Awadé Afoukou *et al.* had found a prevalence of obesity and overweight which was respectively 15.8% and 34.9% [7]. In the United Kingdom, a study had reported a prevalence of obesity estimated at 15% [12]. The very different dietary and lifestyle habits in these countries may explain this disparity. This percentage difference may be due to the increased frequency of maternal diabetes and dietary habits as well as the very different way of life in each country, especially between developed and developing countries [8]-[14].

Concerning the average weight according to the trimester, our study revealed that the average pregnancy-related gain is higher in underweight pregnant women and lower in overweight pregnant women. Pregestational weight status and weight gain during pregnancy therefore evolve in opposite directions. The lower the pre-gestational BMI, the greater the weight gain during pregnancy. In our study, the average weight gain for underweight pregnant women was 9.42 kg VS 8.35 kg for those with a normal BMI. For overweight pregnant women, it was 8.46 Kg VS 7.45 Kg for obese pregnant women. In an effort to optimize the health of mothers and children, in 2009 the United States Institute of Medicine (IOM) revised recommendations for weight gain during pregnancy for the first time since 1990 [4], and these recommendations recommend lower weight gain for women with a high pre-pregnancy body mass index (BMI), particularly for those with a BMI greater than or equal to 30 [3].

On the other hand, some studies conclude that greater than recommended weight gain occurs more frequently in overweight and obese women, which is contradictory with the results of our study [34] [35] [36].

For underweight pregnant women, those with a normal BMI and those overweight then obese, this gain was respectively 9.45 ± 4.2 kg, 8.28 ± 4.11 kg, 8.48 ± 4.74 kg then 7.54 ± 4.00 kg. Our values are lower than those proposed by the IOM. This could be explained by the difference in sample size on the one hand and then by the difference in the dietary habits of the populations on which the studies focused. In the literature, we did not find any studies providing data on optimal weight gain according to BMI.

Maternal and perinatal morbidity and mortality

Pathologies of pregnancy and characteristics of childbirth.

During our study, the pre-existence of excess weight and excessive weight gain during pregnancy were statistically linked to the occurrence of various pathologies that can lead to complications during childbirth. They can be maternal (gestational diabetes, gravid arterial hypertension, difficulties in childbirth) or fetal (outdated term, macrosomia or meconium aspiration) [7]. The risk of occurrence of one of these complications is further increased by significant weight gain during pregnancy [8] [10]. For the WHO, overweight and obesity represent

the fifth risk factor for death worldwide. Regarding the medical history, in our study, the prevalence of overweight pregnant women who had a history was very high and estimated at 83.88%. There is therefore a statistically significant association between excessive weight gain and the occurrence of various pathologies. Similarly, 81.30% of pregnant women had a pathology associated with their previous pregnancy and 84.11% of them had a pathology associated with their current pregnancy. We had found a statistically significant link between hypertension and excessive weight gain. Thus 28.97% of pregnant women with associated hypertension had gained excessive weight with $p < 0.0001$. This link between dysgravidia (gestational hypertension, pre-eclampsia) and excess weight has been widely demonstrated through several studies. The dysgravidies such as gestational arterial hypertension, pre-eclampsia are clearly more frequent in obese and overweight women than in pregnant women of normal weight but statistically unrelated [7]. A study carried out in Cotonou found a prevalence of gestational hypertension at 4.7% in obese patients against 1.6% each in patients of normal weight [7]. These results remain lower than ours, and could be explained by the limitation of our analysis only to pregnant women who gained excessive weight during their pregnancy. Regarding the association of excessive weight gain and pre-eclampsia, our study found a statistically significant association with a prevalence of 08.41% with $p = 0.0001$. These results seem purely logical to us and are explained by the fact that during pregnancy, pre-eclampsia is the first complication of hypertension. According to some authors, the known and undeniable risk factors for gestational hypertension and pre-eclampsia are the mother's age, ethnicity, parity (number of deliveries already carried out) and previous pregnancy history hypertension or pre-eclampsia [37]. A statistically significant association was found between gestational diabetes and excessive weight gain (02.80%) with $p < 0.0001$. Our results remain lower but agree with those of Achille Awadé *et al.* who found a prevalence for gestational diabetes that was higher in overweight pregnant women (17.9%) than in normal weight pregnant women (3.9%) significantly ($p = 0.00$) [7].

Neonatal characteristics

Among the newborns, 03.74% had a prolonged birth term. We did not note any overterm in children born to pregnant women who had gained excessive weight. For the APGAR score, the prevalence of newborns with a score <7 was 13.08% at the first minute. For authors, the prevalence of newborns with an APGAR score ≤ 7 at the first minute and therefore having benefited from resuscitation at birth was higher in overweight and obese pregnant women compared to pregnant women of normal weight [7]. The study in Benin came to the same conclusion [8]. Concerning the birth weight, 84.11% were normal-weighted and 05.60% presented macrosomia. In our study, excessive weight gain during pregnancy significantly increases the risk of macrosomia with $OR = 6.24$ and $p = 0.0009$. Our results agree with the data of some authors. Several studies have shown that overweight women, especially obese women, were more frequently at

risk of giving birth to macrosomic newborns [8] [10] [11]. The frequency of macrosomic fetuses in obese patients is higher (15% - 30%) with a relative risk varying between 2 and 3.82 and a risk of shoulder dystocia multiplied by 3.14 [10]. Forty-six neonates (06.66%) were resuscitated. Forty-seven children or 43.93% of newborns had been transferred, most of them for surveillance 34.57% then 08.41% for fetal asphyxia. All deaths were from perinatal asphyxia.

5. Conclusion

The average weight gain was 9.42 kg for underweight pregnant women, 8.35 kg for pregnant women with a normal BMI, 8.46 kg for overweight pregnant women and 7.45 kg for obese pregnant women. Excessive weight gain is a source of complications during pregnancy, childbirth and postpartum. The profession (civil servant) was associated with excessive weight gain during pregnancy. Pregnant women who had gained excessive weight during pregnancy had a 9 times higher risk of having pregnancy-induced hypertension. They also presented a 6 times higher risk of having pre-eclampsia. The risk of gestational diabetes is also high. There is also a risk of macrosomia and the risk of delivery by cesarean section twice. Higher education and control of weight gain during pregnancy should be systematically integrated into prenatal consultations.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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